REMARKS

These remarks are in response to the Office Action dated September 22, 2003. Claims 3 and 35-37 are pending in the application. No amendments to the claims have been made. Applicants request reconsideration and allowance of the pending claims.

Rejections Under 35 U.S.C. § 101/112, first paragraph

Claims 3, and 35-37 are rejected for lacking utility. This rejection is respectfully traversed. Applicants' grounds for traversal are discussed in three sections below.

1. Interpretation of "broad class of the invention"

Claims 3 and 36 are directed to substantially pure polypeptides that include SEQ ID NO:1. Claims 35 and 37 are directed to substantially pure polypeptides that include SEQ ID NO:2. These polypeptides possess multiple PDZ domains, which are repeat sequences containing a conserved "Gly-Leu-Gly-Phe (GLGF)" amino acid motif (see, *e.g.*, p. 1, lines 13-27 of the specification). The polypeptides bind via the multiple PDZ domains to proteins having a hydrophobic amino acid region consisting of three amino acids represented by Thr/Ser-Xaa-Val at their C-terminus. These binding proteins, referred to as "PDZ domain-binding proteins", are primarily transmembrane proteins reported to play a role in signal transduction, and particularly in cell proliferation, neural transmission, apoptosis, and malignant conversion. Thus, the instantly claimed PDZ domain proteins find specific, substantial, and credible utility as binding partners for the biologically significant PDZ domain-binding transmembrane proteins. As such, the instantly claimed polypeptides serve as valuable targets in the development of pharmaceuticals to combat cell proliferation, apoptosis, and malignant conversion, to name a few (see, *e.g.*, p. 2, line 22-p. 3, line 3).

The Examiner has asserted that the utility of the claimed polypeptides is not specific, stating "what is recited in the instant specification is the biological activities of all PDZ proteins in general and not specifically for the instant proteins." Given the connection between PDZ

domain-binding proteins and disease, there appears to be no dispute that PDZ domain proteins have substantial and credible utility. The question is whether a utility common to the family of PDZ domain proteins (*i.e.*, interacting with PDZ binding transmembrane proteins) is sufficiently specific to meet the criteria of 35 U.S.C. § 101, particularly in light of the U.S. Patent & Trademark Office (U.S.P.T.O.) "Guidelines for Examination of Applications for Compliance with the Utility Requirement" (hereinafter, "the Utility Guidelines" issued in January 2001). The Utility Guidelines promulgate the requirement that a patentable invention either has a well-established utility that is specific, substantial, and credible, or that the invention has a utility that need not be well-established, but is specific, substantial, and credible. The Manual of Patent Examining Procedure (M.P.E.P.) defines "specific utility" as a utility that is specific to the subject matter claimed, in contrast with a "general utility" that is "applicable to the broad class of the invention." M.P.E.P. 2107.01. For example, the use of a polynucleotide as a "gene probe" or "chromosome marker" is not considered to be specific in the absence of disclosure of a specific DNA target. Likewise, an indication that a compound has "useful biological" properties would not be sufficient to define a specific utility for that compound (see the Utility Guidelines at p. 5-6). Applicants respectfully submit that the presently claimed polypeptides have a specific utility. Contrary to the Examiner's suggestion, they are not merely useful as "gene probes" or "chromosome markers" or proteins have "useful biological properties". Rather, the instant specification describes the claimed polypeptides in terms of a specific and significant biological activity (*e.g.*, the ability to interact with PDZ domain-binding transmembrane proteins) and has reasonably correlated that activity with specific disease conditions (*e.g.*, cell proliferation, apoptosis, and malignant conversion). Nevertheless, the Examiner is of the opinion that this activity is not "specific" enough, finding the disclosed activity to be one that is common to "all PDZ proteins in general and not specifically for the instant proteins."

Thus, at issue is the interpretation of the phrase "broad class of the invention" as it applies to a determination of specific utility. Applicants submit that the Examiner's interpretation of "broad class of the invention" as meaning the specific protein family of which the presently claimed polypeptides are members, is overly narrow and improper.

Neither the Utility Guidelines nor the M.P.E.P. provide an express definition of the phrase "broad class of the invention." Thus, we look to the statutory language for suggestion. 35 U.S.C. § 101 defines four statutory "classes" of invention as (1) process, (2) machine, (3) manufacture, or (4) composition of matter. Thus, in the context of utility and § 101, the phrase "broad class of the invention" may reasonably be interpreted to refer to the particular statutory class or category of the invention. Accordingly, in the instant case, the "broad class of the invention" would be compositions of matter. In that context, the use of the claimed polypeptides to target and/or bind PDZ domain-binding transmembrane proteins is a clear utility that is specific to the subject matter claimed and not a general utility applicable to all compositions of matter.

Alternatively, in the context of patent prosecution, the term "class" is frequently used to refer to the U.S. Patent Classification System, more particularly the specific class and subclass into which an invention is categorized. Thus, another reasonable interpretation of the phrase "broad class of the invention" is the category into which an invention is classified. The Examiner previously indicated that the presently claimed polypeptides are classified in Class 530 (Chemistry), Subclass 350 (Proteins of more than 100 amino acid residues) (Restriction Requirement mailed April 25, 2001, Paper No. 7). Accordingly, in the instant case, the "broad class of the invention" would be proteins having more than 100 amino acid residues. In that context, the use of the claimed polypeptides to target and/or bind PDZ domain-binding transmembrane proteins is clearly a utility that is specific to the subject matter claimed and not a general utility applicable to all proteins of more than 100 residues.

As a further alternative, the New Oxford American Dictionary (2001, Oxford University Press) defines the term "class" as "a set or category of things having some property or attribute in common and differentiated from others by kind, type, or quality." More particularly, in the context of biology, the term "class" refers to "a principal taxonomic grouping that ranks above order and below phylum or division." Thus, another reasonable interpretation of the phrase "broad class of the invention" is the taxonomic category into which an invention is classified. According to the structural classification of proteins (SCOP), the PDZ domain family of proteins

is categorized into the class of "beta-proteins" (see, *e.g.*, http://scop.berkeley.edu). As members of the class of beta-proteins, the polypeptides of SEQ ID NOs: 1 and 2 have specific utility as PDZ domain proteins that interact with PDZ domain-binding transmembrane proteins. Moreover, the use of the claimed polypeptides to target and/or bind PDZ domain-binding transmembrane proteins is clearly a utility that is specific to the subject matter claimed and not a general utility applicable to all beta proteins.

All of the above may be considered reasonable interpretations of the phrase "broad class of the invention". In contrast, the Examiner's interpretation is in line neither with the statutory language of 35 U.S.C. § 101, nor with conventions of patent law, nor with the generally accepted definition of the term "class" as it applies to biological compositions of matter. As such, Applicants respectfully submit that the Examiner's interpretation is overly narrow and in error. Moreover, Applicants submit that the use of the claimed polypeptides to target and/or bind PDZ domain-binding transmembrane proteins is not only clearly specific, but substantial and credible as well.

In sum, Applicants respectfully submit that claims 3 and 35-37 meet the criteria of 35 U.S.C. § 101 and that the rejection of these claims under 35 U.S.C. § § 101 and 112, first paragraph, for lack of utility is in error. Accordingly, Applicants request that it be withdrawn.

2. The use of a claimed protein as a liver tissue marker is a well established utility.

The polypeptide of SEQ ID NO:2 is specifically expressed in liver tissue and, therefore, finds separate utility as a liver tissue marker (see, *e.g.*, specification, p. 46-47, Example 5). The Utility Guidelines define a "well established utility" as a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. The fact that a protein is specifically expressed in a limited number of tissues, as is the case herein, certainly suggests to one skilled in the art that it may be used as a tissue marker. Accordingly, the use of the polypeptide of SEQ ID NO:2 as a liver tissue marker meets the criteria for a well-

established utility. This utility is also specific, substantial, and credible, for reasons discussed below.

In the Office Action mailed September 22, 2003 (Paper No. 25, p. 2-3), the Examiner rejects this utility as being either insubstantial or not specific, noting that "the instant specification does not identify any disease or disorder which can be diagnosed by the detection or absence of this protein or which can be treated by the addition or removal of this protein." However, there is no statutory requirement that a marker be associated with disease or therapy for it to have "real world" value. Pathology labs routinely use dyes and such to differentiate between tissues and cell types, to thereby facilitate analyses of clinical samples such as tumor samples. Such markers are not equivalent to "gene probes" and "chromosome markers" because, unlike the latter, polypeptides of SEQ ID NO:2 have specificity (in this case for liver tissue). The Utility Guidelines suggest that the use of a polypeptide as a "gene probe" or "chromosome marker" would be rendered specific upon the disclosure of a specific DNA target. Similarly, the use of a polypeptide as a tissue marker is rendered specific upon disclosure of a specific tissue target.

The Examiner further asserts that "the employment of a protein of the instant invention as a tissue specific marker is not a substantial or specific utility since liver proteins were already known in the art" (Office Action mailed September 22, 2003, Paper No. 25, p. 3). However, it is the claimed invention and not its utility that must be novel. The fact that technological alternatives exist in the art is irrelevant to the issue of patentable utility.

Finally, the Examiner states that all human proteins are either expressed specifically or ubiquitously. Thus, any protein which is expressed in a tissue specific manner can be employed as a tissue marker, such a utility being analogous to the use of a particular protein as a molecular weight marker, a use that is neither specific nor substantial. Applicants respectfully disagree. Contrary to the Examiner's assertion, not all proteins are expressed in a limited number of tissues in a manner that allows them to serve as markers of certain tissues, to the exclusion of other tissues. Such tissue specificity is not as common as the Examiner suggests. Accordingly, it does

not constitute a generic or throw away utility akin to "gene probes" or "chromosome markers" or "molecular weight markers".

In summary, Applicants respectfully submit that the use of the polypeptide of SEQ ID NO:2 as a liver specific tissue marker is a specific, substantial, and credible utility that meets the criteria of 35 U.S.C. § 101.

3. Other well-established utilities

In addition to the reasons set forth above, Applicants submit that the claimed polypeptides satisfy the criteria for utilities which are specific, substantial, credible, and immediately apparent to one skilled in the art.

The claimed polypeptides are members of the family of proteins containing multiple PDZ domains. As discussed in the first paragraph of section 1., above, proteins of this family bind via the multiple PDZ domains to proteins having a hydrophobic amino acid region consisting of three amino acids represented by Thr/Ser-Xaa-Val at their C-terminus, and play a role in signal transduction, and particularly in cell proliferation, neural transmission, apoptosis, and malignant conversion. The Examiner insists that "what is recited in the specification is the biological activities of all PDZ proteins in general and not specifically for the instant proteins." This statement is erroneous with respect to the well-established uses of the claimed polypeptides and the standard for patentability of these compositions.

Example 10 of the Utility Guidelines presents a scenario in which an isolated nucleic acid encoding a specific amino acid sequence is claimed. In this example, the specification discloses that the claimed sequence has a high degree of homology to a sequence encoding a DNA ligase. The Utility Guidelines state

> based on applicant's disclosure and the results of the PTO search, there is no reason to doubt that the assertion that SEQ ID NO:2 encodes a DNA ligase. Further, DNA ligases have well-established use in the molecular biology art based on this class of protein's ability to ligate DNA." (emphasis added).

In this example, the fact that the claimed nucleic acid encodes a putative DNA ligase is sufficient for establishing utility. The Utility Guidelines do not indicate that the specificity of the

putative ligase encoded by the claimed nucleic acid sequence must be known. The utility is deemed sufficient based on the class's ability to perform a function. While it is likely that the DNA ligase encoded by the claimed nucleic acid displays selectivity for a target DNA sequence, patentability of the sequence does not rely on disclosure of this target sequence.

The scenario presented in Example 10 of the Utility Guidelines resembles that of the present case. Applicants have discovered specific sequences and have identified them as members of a family. Furthermore, it is both asserted and known that the members of the family have utility in binding PDZ domain-binding proteins. PDZ domains are modular protein interaction domains. These domains do not interact with any protein, but rather, display selectivity for the C-termini of specific proteins. That Applicants cannot attribute an enzymatic function, however general (*e.g.*, putative DNA ligase activity) to the claimed polypeptides does not render them unpatentable. The binding features of PDZ domain proteins are no less specific or defined than a general enzymatic property such as "DNA ligase." If the Examiner intends to consider the "class" of the claimed polypeptides as PDZ domain proteins for the purposes of patentability (despite the arguments set forth in section 1., above), Applicants note that the disclosure satisfies the standard provided by Example 10 of the Utility Guidelines.

In addition to the uses discussed above, the claimed polypeptides are also useful as tools for determining the specificity of compounds that modulate the functions of other human PDZ domain proteins. This is a clear, specific, and unquestionable utility, and does not require further research to identify or reasonably confirm. Human PDZ proteins are known to play a role in human diseases. For example, a mutation in a PDZ domain protein called harmonin causes Usher syndrome type 1C, an autosomal recessive disorder characterized by blindness and deafness (Verpy *et al.*, *Nat Genet.*, 26(1):51-5, 2000). Many PDZ domain proteins which associate with clinically relevant molecules such as potassium channels and NMDA receptors have been characterized (See, *e.g.*, Kim *et al.*, *Nature*, 378:85-88, 1995; Kornau *et al.*, *Science*, 269:1737-1740, 1995). The utility of screening for a molecule that modulates the binding interactions of these proteins is immediately apparent from these discoveries. Screening requires specificity controls. The claimed polypeptides are useful specificity controls for identifying

compounds that modulate the binding of human PDZ proteins to target proteins. The existence of commercially available protein arrays for assaying binding to PDZ domains is evidence in support of this application. TransSignal™ PDZ Domain Arrays, sold by Panomics, Inc., allow one "to determine whether [a] protein of interest binds to multiple PDZ domains" (p. 4 of TranSignal™ PDZ Domain Arrays Product Manual, copy attached as Exhibit A). The need for specificity controls, and methods of using polypeptides as such was known to the skilled artisan at the time of filing of the present application. This well-established utility does not apply to all unique PDZ domain proteins because each of these proteins displays a different combination of PDZ domains, resulting in unique binding properties. Thus, use of one PDZ domain protein as a specificity control does not obviate the utility of a second PDZ domain protein as a specificity control. The claimed polypeptides clearly have patentable utility. Accordingly, withdrawal of the rejection of claims 35 and 37 is requested.

Enclosed is a $330 check for the Notice of Appeal fee, and a $950 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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